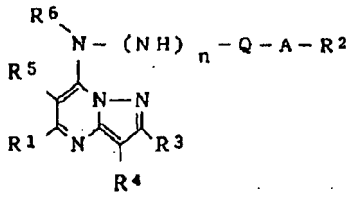
**(57) Abstract**

**Object**

To put forward a nitric oxide synthase inhibitor.

**Method of Solution**

A nitric oxide synthase inhibitor comprising pyrazolo[1,5-a]pyrimidine derivatives represented by general formula as an effective ingredient.



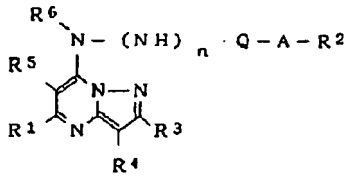
[wherein, $R^1$ denotes a hydrogen atom, substituted or unsubstituted lower alkyl group, cycloalkyl group and the like, $R^2$ denotes a naphthyl group, cycloalkyl group, furyl group, thienyl group and the like, $R^3$ denotes a hydrogen atom, phenyl group or lower alkyl group, $R^4$ denotes a hydrogen atom, lower alkyl group, lower alkoxy carbonyl group, phenyl lower alkyl group and the like, $R^5$ denotes a hydrogen atom or a lower alkyl group, $R^6$ denotes a hydrogen atom, lower alkyl group, phenyl lower alkyl group or substituted benzoyl group, $R^1$ and $R^5$ may link together to form a lower alkylene group; Q denotes a carbonyl group or sulfonyl group, A denotes a single bond, lower alkylene group or lower alkenylene group, and n denotes 0 or 1].

**Patent Claims**

**Claim 1**

A nitric oxide synthase inhibitor containing an effective dose of an effective component comprising pyrazolo[1,5-a]pyrimidine derivatives represented by general formula (1)

[wherein, $R^1$ denotes a hydrogen atom, lower alkyl group optionally having a thienyl group, lower alkoxy group, lower alkylthio group, oxo group or hydroxyl group as a substituent, cycloalkyl group, thienyl group, furyl group, lower alkenyl group or a phenyl group



optionally having 1-3 substituent groups selected fromower alkyl group, lower alkoxy group, phenylthio group and halogen atom, $R^2$ denotes a naphthyl group, cycloalkyl group, furyl group, thienyl group, pyridyl group optionally substituted by halogen atom, phenoxy group optionally substituted by halogen atom, or phenyl group optionally having 1-3 substituent groups selected from lower alkyl group, lower alkoxy group, halogen atom, nitro group, halogen substituted-lower alkyl group, halogen substituted-lower alkoxy group, lower alkoxy carbonyl group, hydroxyl group, phenyl lower alkoxy group, amino group, cyano group, lower alkanoyloxy group, phenyl group and di lower alkoxy phosphoryl lower alkyl group, $R^3$ denotes a hydrogen atom, phenyl group or lower alkyl group, $R^4$ denotes a hydrogen atom, halogen atom, lower alkyl group, lower alkoxy carbonyl group, phenyl lower alkyl group or a phenyl group optionally having a phenylthio group as a substituent, $R^5$ denotes a hydrogen atom or a lower alkyl group, $R^6$ denotes a hydrogen atom, lower alkyl group, phenyl lower alkyl group or a benzoyl group having 1-3 substituent groups selected from lower alkoxy group, halogen substituted-lower alkyl group and halogen atom, and wherein moreover, $R^1$ and $R^5$ may link together to form a lower alkylene group; Q denotes a carbonyl group or sulfonyl group, A denotes a single bond, lower alkylene group or lower alkenylene group, and n denotes 0 or 1]
together with a non-toxic carrier.

**Claim 2**

A nitric oxide synthase inhibitor in accordance with Claim 1, wherein the effective ingredient is the compounds, in general formula in accordance with Claim 1, wherein $R^5$ and $R^6$ are hydrogen atoms, Q is carbonyl group, A is single bond and n is 0.

**Claim 3**

A nitric oxide synthase inhibitor in accordance with Claim 2, wherein the effective ingredient is the compounds, in general formula in accordance with Claim 1, wherein $R^1$ is phenyl group

or lower alkoxy group optionally having hydroxyl group or lower alkoxy group as substituent, $R^2$ is phenyl group having 1-3 groups selected from lower alkoxy group, halogen substituted lower alkyl group and halogen atom as substituent, $R^4$ is a hydrogen atom or phenyl group.

**Claim 4**

A nitric oxide synthase inhibitor in accordance with Claim 2, wherein the effective ingredient is the compounds, in general formula in accordance with Claim 1, wherein $R^1$ is phenyl group, methyl group, ethyl group, n-butyl group or n-pentyl group, and $R^2$ is 4-ethoxy-3,5-dimethoxy phenyl group, 3,4,5-trimethoxy phenyl group, 2-methoxyphenyl group, 2,4-dichlorophenyl group, or 2-trifluoromethyl phenyl group.

**Claim 5**

A nitric oxide synthase inhibitor in accordance with Claim 4, wherein the effective ingredient is selected from 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine, 5-phenyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine and 5-n-butyl-7-(2-trifluoromethyl benzoylamino) pyrazolo[1,5-a]pyrimidine.

**Claim 6**

A nitric oxide synthase inhibitor in accordance with Claim 5, wherein the effective ingredient is 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine.

**Claim 7**

A nitric oxide synthase inhibitor in accordance with any of Claims 1-6 which inhibits inducible-type nitric oxide synthase selectively.

**Claim 8**

Prevention and treatment agent of septicaemia characterised by containing effective dose of the pyrazolo[1,5-a]pyrimidine derivatives in accordance with Claim 1 together with a non-toxic carrier.

**Claim 9**

The endotoxin shock improvement agent characterised by containing effective dose of the pyrazolo[1,5-a]pyrimidine derivatives in accordance with Claim 1 together with a non-toxic carrier.

**Detailed Description of the Invention**

**(0001)**

Technical Sphere of the Invention

This invention relates to a novel NO (nitric oxide) synthase inhibitor, more particularly, a drug which inhibits the induction of inducible-type NO synthase.

**(0002)**

Technology of the Prior Art

In the first half of 1980's, it was discovered for the first time during the study of nitroxide in vivo that NO (nitric oxide) was produced in vivo. Since this discovery, NO attracted attension of many researchers, and it was reported in 1987 that the NO was the main body of vascular endothelium derived relaxing factor. Moreover, presently, physiological function of NO and relation to pathology have been made clear in many fields such as cardiovascular, immunity, nervous system.

**(0003)**

For example, the NO constantly produced in-vivo has been elucidated to play an important role in maintenance of homeostasis of cardiovascular dynamics. Moreover, on the other hand, in septicemia, large quantity of NO is produced from the cytokine activated by endotoxin and this is said to cause endotoxic shock state such as endothelial cell disorder, myocardium contractive force lowering or the like.

**(0004)**

NO is produced from the L-arginine by NO synthase (NOS). Moreover, as the enzyme thereof, by broad classification, there are inducible NOS (iNOS) which is concerned with NO production in pathology and constitutive NOS (cNOS) which is always expressed.

**(0005)**

As described above, because NO participates in various kinds of diseases such as septicemia or the like, research has been carried out into the elucidation of the mechanism thereof and

eventually NOS inhibitor for the purpose of application as therapeutic drug of these diseases. As representative example thereof, arginine analogue such as N-omega-nitro-L-arginine and the like may be proposed.

(0006)
However, most of the NOS inhibitors familiar to the prior art including the aforesaid representative example inhibit cNOS in addition iNOS, and as a result of the use of these as therapeutic agents, even the control of homeostatic cardiovascular dynamics is inhibited, and side effects such as elevation of blood pressure, organ blood flow decrease or the like cannot be avoided. Furthermore, during the use of these, problems such as effects on central nervous system, impotency and the like are also concerned.

(0007)
As above, the NOS inhibitors familiar to the prior art cannot be evaluated as pharmaceutical, and offering of the new substance which can selectively hinder iNOS instead of these is requested in this field.

(0008)
Problems to be Overcome by this Invention
Accordingly, the object of this invention is to put forward nitric oxide synthase inhibitor using substance which could selectively hinder iNOS only desired in this field.

(0009)
Study group of these inventors have been performed research and analysis of the synthesis of various kinds of compound and their pharmacologic actions, with the object of development of drug preparation effective ingredient compound, and in that process, succeeded precedently in synthesis of series of pyrazolopyrimidine derivative having strong analgesia action, and invention concerned with compound such as these or the like was applied (WO95 /35298).

(0010)
In subsequent investigations, these inventors, have made a new discovery, that the fact of aforesaid series of compounds have iNOS induction inhibitory action, separate from their analgesic action and moreover unrelated to that action, and in addition, markedly reduced side

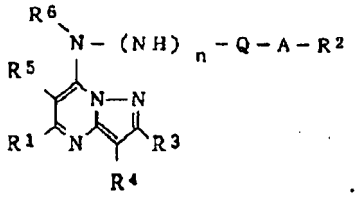
effects. This invention was completed based on this discovery here.

(0011)

Means to Overcome these Problems

In other words, in accordance with this invention, nitric oxide synthase inhibitor is put forward, wherein the effective ingredient comprises the pyrazolo[1,5-a]pyrimidine derivatives which represented by following general formula (1).

(0012)



(0013)

In the aforesaid general formula (1), $R^1$ denotes a hydrogen atom, lower alkyl group optionally having a thienyl group, lower alkoxy group, lower alkylthio group, oxo group or hydroxyl group as a substituent, cycloalkyl group, thienyl group, furyl group, lower alkenyl group or la phenyl group optionally having 1-3 substituent groups selected fromower alkyl group, lower alkoxy group, phenylthio group and halogen atom, $R^2$ denotes a naphthyl group, cycloalkyl group, furyl group, thienyl group, pyridyl group optionally substituted by halogen atom, phenoxy group optionally substituted by halogen atom, or phenyl group optionally having 1-3 substituent groups selected from lower alkyl group, lower alkoxy group, halogen atom, nitro group, halogen substituted-lower alkyl group, halogen substituted-lower alkoxy group, lower alkoxy carbonyl group, hydroxyl group, phenyl lower alkoxy group, amino group, cyano group, lower alkanoyloxy group, phenyl group and di lower alkoxy phosphoryl lower alkyl group, $R^3$ denotes a hydrogen atom, phenyl group or lower alkyl group, $R^4$ denotes a hydrogen atom, halogen atom, lower alkyl group, lower alkoxy carbonyl group, phenyl lower alkyl group or a phenyl group optionally having a phenylthio group as a substituent, $R^5$ denotes a hydrogen atom or a lower alkyl group, $R^6$ denotes a hydrogen atom, lower alkyl group, phenyl lower alkyl group or a benzoyl group having 1-3 substituent groups

selected from lower alkoxy group, halogen substituted-lower alkyl group and halogen atom, and wherein moreover, $R^1$ and $R^5$ may link together to form a lower alkylene group; Q denotes a carbonyl group or sulfonyl group, A denotes a single bond, lower alkylene group or lower alkenylene group, and n denotes 0 or 1.

**(0014)**

The derivatives represented by the aforesaid general formula (1) have a nitric oxide synthate inhibit action, in particular, the action to inhibit inducible-type nitric oxide synthate (iNOS) selectively. Accordingly, it is characterised by the point that it is almost free from side effects such as pressure increase, reduction of blood flow of organs, bad influence to central nervous system and the like.

**(0015)**

As each group in general formula (1) denoting effective ingredient of nitric oxide synthase inhibitor of this invention, for example, each of the following groups can be given as examples. Namely, as lower alkyl group, straight chain or branched chain state lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl group and the like can be given as examples.

**(0016)**

As cycloalkyl group, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl group and the like can be given as examples.

**(0017)**

As lower alkoxy group, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy groups and the like can be given as examples.

**(0018)**

As lower alkyl thio group, methylthio, ethylthio, propylthio, butylthio, pentyl thio, hexyl thio group and the like can be given as examples.

**(0019)**

Fluorine, chlorine, bromine and iodine atom are included in halogen atom.

**(0020)**

As halogen substituted lower alkyl group, trifluoromethyl, pentafluoro ethyl, heptafluoro propyl, nonafluoro butyl, undeca fluoro pentyl, trideca fluoro hexyl group and the like can be given as examples.

**(0021)**

As halogen substituted lower alkoxy group, trifluoromethoxy, pentafluoro ethoxy, heptafluoropropoxy, nonafluoro butoxy, undeca fluoro pentyloxy, trideca fluoro hexyloxy group can be given as examples.

**(0022)**

As lower alkoxycarbonyl group, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxycarbonyl, pentyloxy carbonyl, hexyloxy carbonyl group can be given as examples.

**(0023)**

As dilower alkoxy phosphoryl lower alkyl group, dimethoxyphosphoryl methyl, diethoxy phosphoryl methyl, dipropoxy phosphoryl methyl, diisopropoxy phosphoryl methyl, dibutoxy phosphoryl methyl, dipentyloxy phosphoryl methyl, dihexyl oxy phosphoryl methyl, 2-(dimethoxyphosphoryl) ethyl, 2-(diethoxy phosphoryl) ethyl, 3-(diethoxy phosphoryl) propyl group and the like can be given as examples.

**(0024)**

As naphthyl group, 1-naphthyl, 2-naphthyl group are included.

**(0025)**

As lower alkylene group, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene group and the like can be given as examples.

**(0026)**

As lower alkenylene group, vinylene, propenylene group and the like can be given as examples.

**(0027)**

As pyridyl group optionally substituted by halogen atom, 2-pyridyl, 3-pyridyl, 4-pyridyl, 6-chloro-2-pyridyl, 5-chloro-2-pyridyl, 4-chloro-2-pyridyl, 3-chloro-2-pyridyl, 6-chloro-3-pyridyl, 5-chloro-3-pyridyl, 4-chloro-3-pyridyl, 2-chloro-3-pyridyl, 2-chloro-4-pyridyl, 3-chloro-4-pyridyl, 6-fluoro-3-pyridyl, 6-bromo-3-pyridyl, 6-iodo-3-pyridyl group and the like can be given as examples.

**(0028)**

As phenoxy group optionally substituted by halogen atom, phenoxy, 2-chlorophenoxy, 3-chlorophenoxy, 4-chlorophenoxy, 4-fluoro phenoxy, 4-bromo phenoxy, 4-iodo phenoxy group and the like can be given as examples.

**(0029)**

In thienyl group, 2-thienyl and 3-thienyl group are included, and also 2-furyl and 3-furyl group are included in furyl group.

**(0030)**

As lower alkenyl group, vinyl, allyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl group and the like can be given as examples.

**(0031)**

As phenyl lower alkyl group, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenyl pentyl, 6-phenylhexyl group and the like can be given as examples.

**(0032)**

As phenyl lower alkoxy group, benzyloxy, 2-phenyl ethoxy, 3-phenyl propoxy, 4-phenyl butoxy, 5-phenyl pentyloxy, 6-phenylhexyl oxy group and the like can be given as examples.

**(0033)**

As lower alkanoyloxy group, acetoxy, propionyloxy, butyryl oxy, valeryl oxy, pivaloyloxy, hexanoyloxy, heptanoyloxy group and the like can be given as examples.

**(0034)**

As lower alkyl group optionally having thienyl group, lower alkoxy group, lower alkyl thio group, oxo group or hydroxyl group as substituent, in addition to the aforesaid unsubstituted lower alkyl group, 2-thienylmethyl, 3-thienylmethyl, 1-(2-thienyl) ethyl, 1-(3-thienyl) ethyl, 2-(2-thienyl) ethyl, 2-(3-thienyl) ethyl, 3-(2-thienyl) propyl, 4-(2-thienyl) butyl, 5-(2-thienyl) pentyl, 6-(2-thienyl) hexyl, methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, pentyloxy methyl, hexyloxy methyl, 1-methoxyethyl, 2-methoxyethyl, 3-methoxy propyl, 4-methoxybutyl, 5-methoxy pentyl, 6-methoxy hexyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxy pentyl, 5-hydroxyhexyl, methylthiomethyl, ethylthio methyl, propylthio methyl, butylthio methyl, pentyl thiomethyl, hexyl thiomethyl, 2-methylthio ethyl, 3-methylthio propyl, 4-methylthio butyl, 5-methylthio pentyl, 6-methylthio hexyl, formyl, formylmethyl, acetyl, 2-formyl ethyl, 2-oxopropyl, propionyl, 3-formyl propyl, 3-oxobutyl, 2-oxobutyl, butyryl, 4-formyl butyl, 4-oxo pentyl, 3-oxo pentyl, 2-oxo pentyl, valeryl, 5-formyl pentyl, 5-oxohexyl, 4-oxohexyl, 3-oxohexyl, 2-oxohexyl, hexanoyl group and the like can be given as examples.

**(0035)**

As phenyl group optionally containing 1-3 groups selected from the lower alkyl group, lower alkoxy group, phenylthio group and halogen atom as substituent, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 4-propyl phenyl, 4-butylphenyl, 4-t-butylphenyl, 4-pentylphenyl, 4-hexyl phenyl, 2,3-dimethyl phenyl, 2,4-dimethyl phenyl, 2,5-dimethyl phenyl, 2,6-dimethyl phenyl, 3,4-dimethyl phenyl, 3,5-dimethyl phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxy phenyl, 4-butoxy phenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-bromo phenyl, 4-iodophenyl, 4-fluorophenyl, 4-(phenylthio) phenyl, 3-(phenylthio) phenyl,

2-(phenylthio) phenyl group and the like can be given as examples.

(0036)

As phenyl group optionally containing 1-3 groups selected from the lower alkyl group, lower alkoxy group, halogen atom, nitro group, halogen substituted lower alkyl group, halogen substituted lower alkoxy group, lower alkoxycarbonyl group, hydroxyl group, phenyl lower alkoxy group, amino group, cyano group, lower alkanoyloxy group, phenyl group and dilower alkoxy phosphoryl lower alkyl group as substituent, each of the following group can be given as examples.

(0037)

Namely phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 4-propyl phenyl, 4-butylphenyl, 4-t-butylphenyl, 4-pentylphenyl, 4-hexyl phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-propoxy phenyl, 4-butoxy phenyl, 4-pentyloxyphenyl, 4-hexyloxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, 2,3,5-trimethoxyphenyl, 2,3,6-trimethoxyphenyl, 2,4,5-trimethoxyphenyl, 2,4,6-trimethoxyphenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri ethoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromo phenyl, 3-bromo phenyl, 4-bromo phenyl, 4-iodophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-pentafluoro ethylphenyl, 4-heptafluoro propyl phenyl, 4-nonafluoro butylphenyl, 4-undeca fluoro pentylphenyl, 4-trideca fluoro hexyl phenyl, 2-carbomethoxyphenyl, 3-carbomethoxyphenyl, 4-carbomethoxyphenyl, 4-ethoxycarbonyl phenyl, 4-propoxy carbonyl phenyl, 4-butoxycarbonyl phenyl, 4-pentyloxy carbonyl phenyl, 4-hexyloxy carbonyl phenyl, 2-biphenyl, 3-biphenyl, 4-biphenyl, 2-(diethoxy phosphoryl methyl) phenyl, 3-(diethoxy phosphoryl methyl) phenyl, 4-(diethoxy phosphoryl methyl) phenyl, 4-(dimethoxyphosphoryl methyl) phenyl, 4-(diisopropoxy phosphoryl methyl) phenyl, 3,5-dimethoxy-4-ethoxyphenyl, 3,5-dimethoxy-4-propoxy phenyl, 4-butoxy-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-pentyloxyphenyl, 3,5-dimethoxy-4-hexyloxyphenyl, 2,3-bis (trifluoromethyl) phenyl, 2,4-bis (trifluoromethyl) phenyl, 2,5-bis (trifluoromethyl) phenyl, 2,6-bis (trifluoromethyl) phenyl, 3,4-bis (trifluoromethyl) phenyl,

3,5-bis (trifluoromethyl) phenyl, 3,5-dimethoxy-4-hydroxyphenyl, 3,5-diethoxy-4-hydroxyphenyl, 3,5-dipropoxy-4-hydroxyphenyl, 4-benzyloxy-3,5-dimethoxyphenyl, 4-benzyloxy-3,5-diethoxy phenyl, 3,5-dimethoxy-4-(2-phenyl ethoxy) phenyl, 4-acetoxy-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-propionyloxy phenyl, 2-chloro-3,5-dimethoxyphenyl, 4-chloro-3,5-dimethoxyphenyl, 4-bromo-3,5-dimethoxyphenyl, 3,5-dimethoxy-4-iodophenyl, 3,5-dichloro-4-methoxyphenyl, 3,5-dichloro-4-ethoxyphenyl, 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 2-trifluoromethoxyphenyl, 4-pentafluoro ethoxyphenyl, 4-heptafluoropropoxy phenyl, 4-nonafluoro butoxy phenyl, 4-undeca fluoro pentyloxyphenyl, 4-trideca fluoro hexyloxyphenyl, 3,5-bis (trifluoromethoxy) phenyl, 3,4,5-tris (trifluoromethoxy) phenyl group and the like can be given as examples.

**(0038)**

As phenyl group optionally having phenylthio group as substituent, phenyl, 4-(phenylthio) phenyl, 3-(phenylthio) phenyl, 2-(phenylthio) phenyl group and the like can be given as examples.

**(0039)**

As benzoyl group containing 1-3 groups selected from the lower alkoxy group, halogen substituted lower alkyl group and halogen atom as substituent, 2-chlorobenzoyl, 3-chlorobenzoyl, 4-chlorobenzoyl, 2-fluorobenzoyl, 2-bromobenzoyl, 2-iodobenzoyl, 2,4-dichlorobenzoyl, 3,4-dichlorobenzoyl, 2,5-dichlorobenzoyl, 2,6-dichlorobenzoyl, 2-trifluoromethyl benzoyl, 3-trifluoromethyl benzoyl, 4-trifluoromethyl benzoyl, 3, 5-bis (trifluoromethyl) benzoyl, 3, 4, 5-tris (trifluoromethyl) benzoyl, 2-methoxybenzoyl, 3-methoxybenzoyl, 4-methoxybenzoyl, 2,3-dimethoxybenzoyl, 2,4-dimethoxybenzoyl, 3,5-dimethoxybenzoyl, 3, 4, 5-trimethoxy benzoyl, 2-ethoxy benzoyl, 2-propoxy benzoyl, 2-butoxy benzoyl, 2-pentyloxy benzoyl, 2-hexyloxy benzoyl group and the like can be given as examples.

**(0040)**

The pyrazolo[1,5-a]pyrimidine derivatives represented by aforesaid general formula (1) are useful for prevention and therapy of septicaemia, endotoxin shock, chronic rheumatoid

arthritis and the like as a nitric oxide synthate, in particularly for a drug inhibiting the inducible type nitric oxide synthate (iNOS), and it has an advantage that it is almost free from the side effect which is seen in the prior art nitric oxide synthate.

**(0041)**

Compounds wherein $R^5$ and $R^6$ are hydrogen atoms, Q is carbonyl group, A is single bond, and n is 0 can be given as examples of the preferred pyrazolo[1,5-a]pyrimidine derivatives as the aforesaid nitric oxide synthase inhibitor. Among the said compounds, particularly compounds wherein $R^1$ is phenyl group or lower alkyl group optionally-containing hydroxyl group or lower alkoxy group as substituent, $R^2$ is phenyl having, as substituent, 1-3 groups selected from lower alkoxy group, halogen substituted lower alkyl group and halogen atom and $R^4$ is hydrogen atom or phenyl group, and more embodiment, compound wherein $R^1$ is phenyl group, methyl group, ethyl group, n-butyl group or n-pentyl group and $R^2$ is 4-ethoxy-3,5-dimethoxyphenyl group, 3, 4, 5-trimethoxyphenyl group, 2-methoxyphenyl group, 2,4-dichlorophenyl group or 2-trifluoromethylphenyl group is particularly preferred.

**(0042)**

As embodiment of such preferred pyrazolo[1,5-a]pyrimidine derivatives, for example 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine, 5-phenyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine and 5-n-butyl-7-(2-trifluoromethyl benzoylamino) pyrazolo[1,5-a]pyrimidine can be given as examples, and among these, 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine is the most ideal.

**(0043)**

Effective ingredient compound represented by general formula (1) of this invention can be produced using various processes, and, as embodiment thereof, for example, process in accordance with the aforesaid WO95 /35298 bulletin can be given as example.

**(0044)**

Typically, this method can be carried out in a process wherein 7-hydroxy pyrazolo[1,5-a] pyrimidine species are obtained by condensation reaction of 3-aminopyrazole yl and suitable carboxylate ester, then this is halogenated to make 7-halopyrazolo[1,5-a]pyrimidine species,

and this is further treated with ammonia water or hydrazine, to convert into 7-amino compound, and by reacting this with an acid halide.

**(0045)**

As the embodiment example of effective ingredient compound of this invention obtained such processes, each compound shown as Examples No. 1-134 in accordance with later described Tables 1-5 for example can be given as example.

**(0046)**

Each compound represented by general formula (1) can be made into the acid addition salt which is pharmacologically permitted, and such salts or the like is also included as effective ingredient compound of nitric oxide synthase inhibitor of this invention. As the acid which can form the aforesaid acid addition salt, inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid or the like, organic acid such as oxalic acid, fumaric acid, maleic acid, tartaric acid, citric acid or the like can be given as examples, and formation reaction of this acid addition salt can follow normal method.

**(0047)**

Moreover, in accordance with normal methods, otherwise the ones wherein, in compounds represented by aforesaid general formula (1), $R^6$ is hydrogen atom, can be made into alkali metal salt, for example sodium salt, potassium salt and the like, alkaline earth metal salt, for example calcium salt, magnesium salt and the lik, and other salt such as cuprate or the like, are also included as effective ingredient compound of nitric oxide synthase inhibitor of this invention.

**(0048)**

Moreover, among compounds represented by general formula (1), some of the compounds wherein $R^1$ is lower alkenyl group, and compounds wherein A is alkenylene group can take cis, trans isomer structure, the nitric oxide synthase inhibitor of this invention can include any such isomers as an active ingredient.

**(0049)**

Moreover, for some of the compounds represented by general formula (1), the optical isomer with carbon atom as asymmetric center is present, and nitric oxide synthase inhibitor of this invention can contain as an active ingredient any such optically active substance and racemate.

**(0050)**

The nitric oxide synthase inhibitor of this invention is made into a general drug preparation composition using the compound represented by general formula (1) together with the suitable non-toxic carrier, and used.

**(0051)**

As the aforesaid carrier used for drug preparation of this invention, corresponding to conditions of use of preparation, usually used diluent or excipient such as filler, expander, binding agent, humectant, disintegrating agent, surface active agent, lubricant can be given as example and these are suitably selected and used corresponding to administration unit form of preparation to be obtained.

**(0052)**

As administration unit form of the aforesaid drug preparation, various forms can be selected corresponding to therapy objective, and, as representative examples thereof, tablet, pill, powder, liquid agent, suspension, emulsion, granule, encapsulated formulation, suppository, injection (liquid agent, suspension or the like), ointment and the like may be proposed.

**(0053)**

When forming into tablet, as the aforesaid preparation carrier, for example excipient such as lactose, refined sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silica, potassium phosphate and the like, binding agent such as water, ethanol, propanol, single syrup, glucose liquid, starch liquid, gelatin solution, carboxymethylcellulose, hydroxypropylcellulose, methyl cellulose, polyvinylpyrrolidone and the like, disintegrating agent such as carboxymethylcellulose sodium, carboxymethylcellulose calcium, low degree of substitution hydroxypropylcellulose, dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate and the like, surfactant

such as polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride and the like, inhibitor of disintegration such as refined sugar, stearin, cacao butter, hydrogenated oil or the like, adsorption enhancer such as quaternary ammonium salt group, sodium lauryl sulfate and the like, moisture retaining agent such as glycerol, starch and the like, adsorbent such as starch, lactose, kaolin, bentonite, colloidal silica or the like, lubricant such as purified talc, stearate, boric acid powder, polyethyleneglycol and the like can be used. Further the tablet can be made into the tablet coated with ordinary agent coating in accordance with requirements, for example sugar coated tablet, gelatin encapsulation tablet, enteric coated tablet, film coating tablet or double tablet, multilayer tablet.

**(0054)**

When formed into the form of a pill, excipient such as for example carrier such as glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc and the like, binding agent such as powdered gum arabic, tragacanth powder, gelatin, ethanol and the like, disintegrating agent such as laminaran, agar and the like can be used as preparation carrier.

**(0055)**

When formed into a form of suppository, as preparation carrier, for example polyethyleneglycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin, semi-synthetic glyceride and the like can be used.

**(0056)**

Encapsulated formulation is usually prepared according to normal method, by mixing effective ingredient compound of this invention with the various preparation carrier exemplified above and packing into hard gelatin capsule, soft capsule and the like.

**(0057)**

When prepared as injection agent such as liquid agent, emulsion, suspension and so on, such materials are sterilized and preferably made isotonic with blood, and when formed into such forms, as a diluent, for example, water, ethanol, macrogol, propylene glycol, ethoxylation isostearyl alcohol, polyoxyisosteary alcohol, polyoxyethylene sorbitan fatty acid ester species as can be used. Moreover, in this case, sufficient sodium chloride, dextrose or glycerol to

form an isotonic solution may be contained in agent of this invention, and moreover ordinary solubilizer, buffer agent, analgesic or the like may be added.

**(0058)**

Furthermore, in agent of this invention, colorant, preservative, odorant, flavor agent, sweetener and so on and other pharmaceutical can be contained in accordance with requirements.

**(0059)**

When formed into a form of ointment such as paste, cream, gel and the like, for example white petrolatum, paraffin, glycerol, cellulose derivative, polyethyleneglycol, silicone, bentonite and the like can be used as diluent.

**(0060)**

The amount of effective ingredient compound represented by general formula (1) to be contained in the agent of this invention is suitably selected from a wide range without restriction in particular, but usually one containing an amount of about 1-70 wt.% approximately in the drug preparation is satisfactory.

**(0061)**

Administration method of the aforesaid drug preparation is not limited in particular, and it is determined corresponding to various formulations, age of patient, the distinction of sex, other conditions, degree of disease or the like. For example, tablet, pill, liquid agent, suspension, emulsion, granule and encapsulated formulation are administered orally, and injection is used alone or mixed with ordinary adjuvant fluid such as dextrose, amino acid or the like, and administered intravenously, and further it is administered alone intramuscularly, intracutaneously, subcutaneously or intraperitoneally in accordance with requirements, and, the suppository is administered rectally.

**(0062)**

The dose of the aforesaid drug preparation is suitably selected by using the method of use thereof, age of patient, the distinction of sex, other conditions, degree of disease or the like,

but usually the amount of the compounds of this invention which are effective ingredient of about 0.5-20 mg per 1 kg bodyweight per day is satisfactory, and said preparation can be administered by being divided 1-4 times per day.

(0063)

**Examples**

Hereinafter, in order to describe this invention further in detail, Preparation Examples of nitric oxide synthase inhibitor of this invention is given and thereafter, Pharmacological Test Examples are shown.

(0064)

**Preparation Example 1**

Preparation of encapsulated formulation.

Using 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine as effective ingredient compound, hard gelatin capsules (1000 capsules) containing 250 mg per 1 capsule was prepared by the following formulation.

(0065)

| | |
|---|---|
| Effective ingredient compound | 250 g |
| Crystalline cellulose (Pharmacopeia of Japan product) | 30 g |
| Corn starch (Pharmacopeia of Japan product) | 17 g |
| Talc (Pharmacopeia of Japan product) | 2 g |
| Magnesium stearate (Pharmacopeia of Japan product) | 1 g |

In other words, each component was made into fine powder in accordance with aforesaid formulation, it was sufficiently mixed to form a uniform mixture, thereafter this was packed in gelatin capsule for the oral administration having desired dimension and the target encapsulated formulation was prepared.

(0066)

**Preparation Example 2**

Preparation of tablet.

Using 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine as effective ingredient compound, tablets (2000 tablets) containing 300 mg per tablet was prepared by the following formulation.

(0067)

| | |
|---|---|
| Effective ingredient compound. | 600 g |
| Lactose (Pharmacopeia of Japan product) | 67 g |
| Corn starch (Pharmacopeia of Japan product) | 33 g |
| Carboxymethylcellulose calcium (Pharmacopeia of Japan product) | 25 g |
| Methyl cellulose (Pharmacopeia of Japan product) | 12 g |
| Magnesium stearate (Pharmacopeia of Japan product) | 3 g |

In other words, effective ingredient compound, lactose, corn starch and carboxymethylcellulose calcium were mixed thoroughly according to the aforesaid formulation, and the mixture was granulated using methyl cellulose aqueous solution and was passed through sieve of 24 mesh, and this was mixed with magnesium stearate and was pressed to tablet, and the target tablet was prepared.

(0068)

**Preparation Example 3**

Preparation of encapsulated formulation

Using 5-n-butyl-7-(2-trifluoromethyl benzoylamino) pyrazolo (1,5-a) pyrimidine, as effective ingredient, hard gelatin capsules (2000) containing 200 mg thereof per 1 capsule was prepared with the following formulation.

(0069)

| | |
|---|---|
| Effective ingredient compound | 400 g |
| Crystalline cellulose (Pharmacopeia of Japan product) | 60 g |
| Corn starch (Pharmacopeia of Japan product) | 34 g |
| Talc (Pharmacopeia of Japan product) | 4 g |
| Magnesium stearate (Pharmacopeia of Japan product) | 2 g |

In other words, each component was made into fine powder in accordance with aforesaid

formulation, it was sufficiently mixed to form a uniform mixture, thereafter this was packed in gelatin capsule for the oral administration having desired dimension and the target encapsulated formulation was prepared.

**(0070)**

**Preparation Example 4**

Preparation of tablet.

Using 5-n-butyl-7-(2-trifluoromethyl benzoylamino) pyrazolo[1,5-a]pyrimidine as effective ingredient compound, tablets (2000 tablets) containing 300 mg thereof per tablet was prepared by the following formulation.

**(0071)**

| | |
|---|---|
| Effective ingredient compound. | 600 g |
| Lactose (Pharmacopeia of Japan product) | 67 g |
| Corn starch (Pharmacopeia of Japan product) | 33 g |
| Carboxymethylcellulose calcium (Pharmacopeia of Japan product) | 25 g |
| Methyl cellulose (Pharmacopeia of Japan product) | 12 g |
| Magnesium stearate (Pharmacopeia of Japan product) | 3 g |

In other words, effective ingredient compound, lactose, corn starch and carboxymethylcellulose calcium were mixed thoroughly according to the aforesaid formulation, and the mixture was granulated using methyl cellulose aqueous solution and was passed through sieve of 24 mesh, and this was mixed with magnesium stearate and was pressed to tablet, and the target tablet was prepared.

**(0072)**

**Pharmacological Test Example 1**

Wistar strain male rat (8 weeks old, 200-250 g) was slaughtered by cervical spine dislocation, and thoracic aorta was extracted promptly, and surrounding connective tissue was peeled off. Next, intravascular cavity was abraded using cotton yarn, thereby eliminating endothelial cells in order to eliminate the effect of cNOS present in vascular endothelial cells, and this was cut into 2 mm length, and ring-form sample was prepared. This sample was suspended in an organ bath filled with 10 ml of Krebs-Henseleit liquid (NaCl 118 mM, KCl 4.7 mM,

CaCl2 2.5 mM, KH2PO4 1.2 mM, $MgSO_4$ 1.2 mM, NaHCO3 25 mM and glucose 11 mM) under pressure of 1 g, and O2/CO2 (95 %/5 %) mixed gas was aerated continuously.

**(0073)**

Firstly, about this sample, it was confirmed that after having been contracted blood vessel by adding phenylephrine 3x10[-7]M, no relaxation occurred in any of the cases when acetylcholine 10[-5]M was added and when L-arginine 10[-5]M was added, namely both of cNOS and iNOS were lacked.

**(0074)**

Next, lipopolysaccharide (LPS) 300 ng/ml was added to the aforesaid sample, and later, L-arginine 10[-5]M was added, and relaxation and cyclic GMP (cGMP) concentration of blood vessel were measured (control group).

**(0075)**

On the other hand, 3x10[-5]M of 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine (compound of Example 1 in Table 1) was added to organ bath 30 minutes before the addition of LPS, and relaxation of blood vessel and cGMP concentration after the addition of L-arginine were measured in the same way as described above (group of this invention).

**(0076)**

Moreover, constriction and relaxation of blood vessel were measured by isotonic transducer (TD-111T, made by Nihon Kohden) and it was recorded with a recorder (NIHON DENSI KAGAKU, U-228). Moreover, cGMP concentration was measured with commercial radioimmunoassay kit (Amersham, cGMP[125I] assay system).

**(0077)**

As a result, in group of this invention, relaxation of blood vessel was inhibited 70 % compared with control group. Moreover, cGMP concentration was inhibited 80 % in group of this invention compared with control group.

**(0078)**

Therefore it is clear that effective ingredient compound of this invention inhibited the induction of iNOS by LPS.

(0079)

**Pharmacological Test Example 2**

Wistar strain male rat (8 weeks old, 200-250 g) was slaughtered by cervical spine dislocation, and thoracic aorta was extracted promptly, and surrounding connective tissue was peeled off. Blood vessel was incubated in HEPES•Hanks' solution (CaCl2•H2O 185.5 mg/l, Kcl 400.0 mg/l, KH2PO4 60.0 mg/l, $MgSO_4$ 97.7 mg/l, NaCl 8000.0 mg/l, NaHCO3 350.0 mg/l, Na2HPO4 47.5 mg/l, glucose 1000 mg/l) containing collagenase 238 U/ml, esterase 22.5 U/ml and bovine serum albumin 0.2 % at 37°C for 45 minutes.

(0080)

Next, endothelial cell and adventitia were peeled from this blood vessel in HEPES•Hanks' solution, and only tunica media smooth muscle was withdrawn, cut finely, incubated at 37°C in HEPES•Hanks' solution containing collagenase, esterase and bovine serum albumin which was the same as aforesaid solution for 70 minutes, and caused to enzymatic digestion. This was suspended in Dulbecco modified process Eagle culture medium ($MgSO_4$•7H2O 200.0 mg/l, NaCl 6400 mg/l, NaHCO3 3700.0 mg/l, NaH2PO4 125.5 mg/l, $Fe(NO_3)3$•9H2O 0.1 mg/l, phenol red 15.0 mg/l, folic acid 4.0 mg/l, nicotinamide 4.0 mg/l, calcium pantothenate 4.0 mg/l, pyridoxal /Hcl 4.0 mg/l, riboflavin 0.4 mg/l, thiamine•HCl 4.0 mg/l, choline chloride 4.0 mg/l, glucose 1000 mg/l, 1-inositol 7.0 mg/l, pyruvic acid sodium 110.0 mg/l) containing fetal bovine serum 10 %, and it was washed several times, and it was seeded to dish with rate of 2 x $10^5$/ml. Cells were subcultured at the time when they became confect, and they were used to the next experimentat the fourth generation.

(0081)

In other words, L-arginine 10[-5]M was added to the aforesaid cultured cell, and further LPS 300 ng/ml or interleukin-1β (IL-1β) 10 ng/ml was added, and it was left to stand for 24 hours, and the amount of accumulated NO2 was measured (control group).

(0082)

On the other hand, 30 minutes before the addition of LPS or IL-1β, 3x10[-5]M of 5-n-butyl-7-(3,4,5-trimethoxy benzoylamino) pyrazolo[1,5-a]pyrimidine (compound of Example 1 in Table 1, group 1 of this invention) or 3x10[-5]M of 5-n-butyl-7-(2-trifluoromethyl benzoylamino) pyrazolo[1,5-a]pyrimidine (compound of Example 32 in Table 1, group 2 of

this invention) was added to organ bath, and in the same way as described above, thee amount of accumulated NO2 at 24 hours after the addition of L-arginine or IL-1β was measured (group of this invention).

(0083)

Moreover, the amount of NO2 was determined by a process wherein Griess reagent (0.1 % N-[1-naphthyl] ethylenediamine • dihydrochloride / H2O + 1 % sulphanyl amine / 2.5 % $H3PO_4$) was added in an equivalent amount to medium supernatant and absorbance at 570 nm was measured.

(0084)

The results are shown in Figure 1 and Figure 2.

(0085)

Moreover, Figure 1 shows the data at having been added LPS and Figure 2 denotes data at having been added IL-1β respectively. Moreover, in each Figure, data of the group without being added is shown together as control.

(0086)

From Figure 1 and Figure 2, it is cleared that effective ingredient compound of this invention inhibited the induction of iNOS by LPS and IL-1β.

(0087)

**Pharmacological Test Example 3**

Spraque Dawley strain male rat (6-9 weeks old, 200-250 g) were slaughtered by cervical spine dislocation, and thoracic aorta was extracted promptly, and surrounding connective tissues were peeled off. Next, the aorta was cut into 5-7 rings, each was sliced open longitudinally, and thereafter intravascular cavity was abraded using a washed swab thereby eliminating endothelial cells in order to eliminate the effect of cNOS present in vascular endothelial cells, and sample was prepared.

(0088)

The aforesaid sample was introduced into Krebs-Henseleit liquid (the same composition as the one used in Pharmacological Test Example 1) wherein dimethylsulfoxide solution of

effective ingredient compound of this invention (test compound) which was prepared in 30 μM concentration was added and L-arginine was further added so as to become μM concentration, and the mixture was incubated at 37°C for 30 minutes. Continuing lipopolysaccharide (LPS) was added by 1000 ng/ml concentration, and it was incubated at 37°C for 24 hours (experimental group using test compound, group of this invention).

(0089)

Next, supernatant was sampled on 96-well plate, and NO2 was coloured with Griess liquid according to NO2 measurement method described in literature (New Biochemistry Experiment chair 10, blood vessel, endothelium and smooth muscle, 135 pages, Jpn Biochem Soc Eds, Tokyo Kagaku Dojin, 1993) and it was measured using Biokinetics Reader (EL-340 model, made by BIO-TEK Instruments company), and accumulated NO2 amount was calculated.

(0090)

Moreover, the sample of blood vessel piece was dissolved in 1N sodium hydroxide aqueous solution, and it was coloured with Bio-Rad DC protein assay kit (made by Bio-Rad Laboratories Co) and it was measured with spectrophotometer (made by HITACHI Co, U-3000 model), and protein content was calculated. Moreover, from these values, the quantity of NO2 formed per protein 1 mg was determined.

(0091)

On the other hand, the same test was carried out for the control group with the addition of dimethylsulfoxide instead of the test compound for the negative control group without even the addition of LPS.

(0092)

The iNOS induction inhibition rate was determined according to the following equation from NO2 quantity formed per protein 1 mg in each group obtained as above.

(0093)

Inhibition rate (%) ={1- [(this invention group value) - (negative control group value)] / [control group value) - (negative control group value)]} x 100

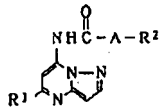
The obtained results are shown in the Table 6.

**(0094)**

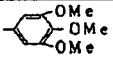
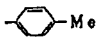
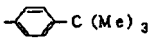
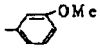
From Table 6, it is clear that the effective ingredient compounds of this invention inhibited the induction of iNOS by LPS.

**(0095)**

Table 1

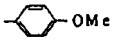
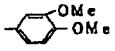
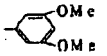
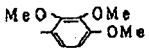
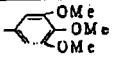
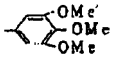
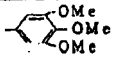
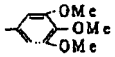
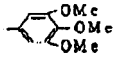


Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, nPe: n-pentyl group, Ph: Phenyl group

| Example No. | R1 | R2 | A | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|
| 1 | nBu |  | Single bond | 127-129 (diethylether – n-hexane) |
| 2 | nBu | Ph | Single bond | 83-85 (ethyl acetate – n-hexane) |
| 3 | nBu |  | Single bond | 102-104 (n-hexane) |
| 4 | nBu |  | Single bond | 94-95 (n-hexane) |
| 5 | nBu |  | Single bond | 83-84 (n-hexane) |
| 6 | nBu |  | Single bond | $^1$H-NMR (CDCl$_3$) 0.97(3H,t,J=7.3), 1.37(9H,s), 1.4-1.5(2H,m), 1.7-1.8(2H,m), 2.86(2H,t,J=7.8), 6.57(1H,d,J=2.3), 7.58(1H,d,J=8.7), 7.77(1H,s), 7.97(1H,d,J=8.7), 8.03(1H,d,J=2.3), 10.0(1H,brs) |
| 7 | nBu |  | Single bond | 82-84 (n-hexane) |
| 8 | nBu |  | Single bond | 49-51 (n-hexane) |

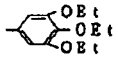
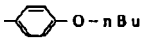
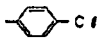
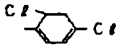
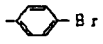
**(0096)**

Table 1 (continued)

| Example No. | R1 | R2 | A | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|
| 9 | nBu |  | Single bond | 108-109 (n-hexane) |
| 10 | nBu |  | Single bond | 129-132 (n-hexane) |
| 11 | nBu |  | Single bond | 143-144 (diethylether – n-hexane) |
| 12 | nBu |  | Single bond | 101-103 (diethylether – n-hexane) |
| 13 | nBu |  | Single bond | 92-94 (diethylether – n-hexane) |
| 14 | nBu |  | Single bond | 115-117 (ethyl acetate – n-hexane) |
| 15 | Et |  | Single bond | 141-143 (ethyl acetate – n-hexane) |
| 16 | nPr |  | Single bond | 119-121 (diethylether – n-hexane) |
| 17 |  |  | Single bond | 198-201 (ethyl acetate – n-hexane) |
| 18 | nPe |  | Single bond | 116-118 (n-hexane) |
| 19 | Ph |  | Single bond | 185-187 (ethyl acetate – n-hexane) |

(0097)

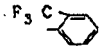
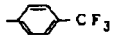
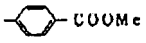
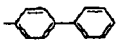
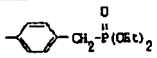
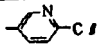
Table 1 (continued)

| Example No. | R1 | R2 | A | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|
| 20 | nBu |  | Single bond | 100-102 (diethylether – n-hexane) |
| 21 | nBu |  | Single bond | 87-90 (n-hexane) |
| 22 | nBu |  | Single bond | 99-100 (n-hexane) |
| 23 | nBu |  | Single bond | 107-109 (diethylether) |
| 24 | nBu |  | Single bond | 81-82 (n-hexane) |
| 25 | nBu |  | Single bond | 92-94 (diethylether) |
| 26 | nBu |  | Single bond | 97-99 (n-hexane) |
| 27 | nBu |  | Single bond | 93-95 (n-hexane) |
| 28 | nBu |  | Single bond | 97-99 (n-hexane) |
| 29 | nBu |  | Single bond | 133-135 (ethyl acetate – n-hexane) |
| 30 | nBu |  | Single bond | 143-145 (ethyl acetate – n-hexane) |

(0098)

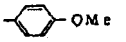
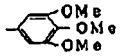
Table 1 (continued)

| Example No. | R1 | R2 | A | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|
| 31 | Et |  | Single bond | 125-127 (diethylether – n-hexane) |
| 32 | nBu |  | Single bond | 84-87 (n-hexane) |
| 33 | nBu |  | Single bond | 95-97 (n-hexane) |
| 34 | nBu |  | Single bond | 122-123 (n-hexane) |
| 35 | nBu |  | Single bond | 139-141 (ethyl acetate – n-hexane) |
| 36 | nBu |  | Single bond | 119-121 (ethyl acetate – n-hexane) |
| 37 | nBu |  | Single bond | 57-60 (ethyl acetate – n-hexane) |
| 38 | nBu |  | Single bond | 82-84 (diethylether – n-hexane) |
| 39 | nBu |  | Single bond | 103-105 (ethyl acetate – n-hexane) |
| 40 | nBu |  | Single bond | 92-93 (diethylether – n-hexane) |
| 41 | nBu | Ph | $-CH_2-$ | 80-82 (diethylether – n-hexane) |

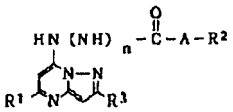
(0099)

Table 1 (continued)

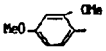
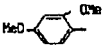
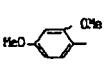
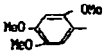
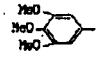
| Example No. | R1 | R2 | A | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|
| 42 | nBu |  | $-CH_2-$ | 73-75 (diethylether – n-hexane) |
| 43 | nBu | Ph | $-C_2H_4-$ | $^1H$-NMR (CDCl$_3$) 0.95(3H,t,J=7.3), 1.3-1.5 (2H,m), 1.7-1.8(2H,m), 2.80 (2H,t,J=7.8), 2.88(2H,t,J=7.5), 3.09(2H,t,J=7.5), 6.53 (1H,d,J=2.2), 7.2-7.3(5H,m), 7.60(1H,s), 7.95(1H,d,J=2.2), 9.23(1H,brs) |
| 44 | nBu | PhO- | $-CH_2-$ | 108-109 (n-hexane) |
| 45 | nBu |  | $-CH_2-$ | 140-142 (ethyl acetate – n-hexane) |
| 46 | nBu |  | -CH=CH- | 134-137 (ethyl acetate – n-hexane) |

**(0100)**

Table 2



Me: methyl group, Et: ethyl group, nPr: n-propyl group,
nBu: n-butyl group, tBu: t-butyl group, nPe: n-pentyl group,
Ph: Phenyl group, Ac: Acetyl group.

| Example No. | R1 | R2 | R3 | A | n | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|
| 47 | nBu |  | H | Single bond | 0 | $^1$H-NMR (CDCl$_3$) 0.95(3H,t,J=7.4), 1.2-2.1 (14H,m), 2.4-2.6(1H,m),2.81 (2H,t,J=7.8), 5.54(1H,d,J=2.2),7.02(1H,s), 8.00(1H,d, J=2.2),8.29(1H,brs) |
| 48 | nBu |  | H | Single bond | 0 | 141-142 (ethanol – n-hexane) |
| 49 |  |  | H | Single bond | 0 | 209-211 (methylene chloride – ethyl acetate) |
| 50 |  |  | H | Single bond | 0 | 206-208 (methylene chloride – ethyl acetate) |
| 51 | nBu |  | H | Single bond | 0 | 136-137 (ethanol – n-hexane) |
| 52 | Me |  | H | Single bond | 0 | 173-175 (ethanol – n-hexane) |
| 53 | nBu |  | Me | Single bond | 0 | 127-129 (ethanol – n-hexane) |
| 54 | $CH_2$=CH-$C_2H_4$- |  | H | Single bond | 0 | 104-106 (ethyl acetate – n-hexane) |

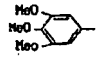
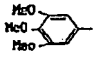
 

**(0101)**

Table 2 (continued)

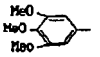
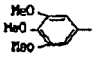
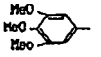
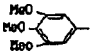
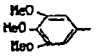
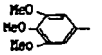
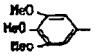
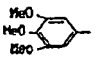
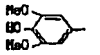
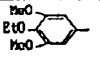
| Example No. | R1 | R2 | R3 | A | n | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|
| 55 | Et-O-$CH_2$- |  | H | Single bond | 0 | 138-140 (ethyl acetate – n-hexane) |
| 56 |  |  | H | Single bond | 0 | 163-165 (chloroform – ethyl acetate) |
| 57 |  |  | H | Single bond | 0 | 166-168 (ethyl acetate – n-hexane) |
| 58 |  |  | H | Single bond | 0 | 193-195 (methylene chloride - diethylether) |
| 59 |  |  | H | Single bond | 0 | 174-176 (methylene chloride - diethylether) |
| 60 |  |  | H | Single bond | 0 | 203-205 (methylene chloride - diethylether) |
| 61 |  |  | H | Single bond | 0 | 175-177 (methylene chloride - ethyl acetate) |
| 62 |  |  | H | Single bond | 0 | 192-194 (methylene chloride - diethylether) |
| 63 |  |  | H | Single bond | 0 | 181-193 (methylene chloride - diethylether) |
| 64 |  |  | H | Single bond | 0 | 224-226 (methylene chloride - diethylether) |

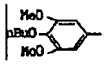
 

| | | | | | | |
|---|---|---|---|---|---|---|
| 65 |  |  | H | Single bond | 0 | 214-216 (methylene chloride - diethylether) |

**(0102)**

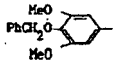
Table 2 (continued)

| Example No. | R1 | R2 | R3 | A | n | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|
| 66 |  |  | H | Single bond | 0 | 190-192 (methylene chloride - diethylether) |
| 67 |  |  | H | Single bond | 0 | 222-224 (chloroform – ethyl acetate) |
| 68 |  |  | H | Single bond | 0 | 193-195 (chloroform – ethyl acetate) |
| 69 |  |  | H | Single bond | 0 | 189-191 (methylene chloride - diethylether) |
| 70 |  |  | H | Single bond | 0 | 174-176 (methylene chloride - diethylether) |
| 71 |  |  | H | Single bond | 0 | 191-193 (methylene chloride - diethylether) |
| 72 |  |  | H | Single bond | 0 | 198-200 (methylene chloride - ethyl acetate) |
| 73 |  |  | H | Single bond | 0 | 157-159 (ethyl acetate) |
| 74 | nBu |  | H | Single bond | 0 | 159-161 (ethanol – n-hexane) |
| 75 | nBu |  | H | Single bond | 0 | 79-81 (diethylether – n-hexane) |

| | | | | | | |
|---|---|---|---|---|---|---|
| 76 | nBu |  | H | Single bond | 0 | 98-100 (n-hexane) |

(0103)

Table 2 (continued)

| Example No. | R1 | R2 | R3 | A | n | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|
| 77 | nBu |  | H | Single bond | 0 | 82-85 (ethanol – n-hexane) |
| 78 | nBu |  | H | Single bond | 0 | 158-160 (ethyl acetate – n-hexane) |
| 79 | nBu |  | H | Single bond | 0 | 182-184 (ethyl acetate – n-hexane) |
| 80 | nBu |  | H | Single bond | 0 | 132-135 (ethyl acetate – n-hexane) |
| 81 | nBu |  | H | Single bond | 0 | 111-113 (diethylether – n-hexane) |
| 82 | Me |  | H | Single bond | 0 | 154-155 (ethanol – n-hexane) |
| 83 | nPr |  | H | Single bond | 0 | 139-141 (diethylether – n-hexane) |
| 84 |  |  | H | Single bond | 0 | 102-104 (n-hexane) |
| 85 | nPe |  | H | Single bond | 0 | 93-95 (n-hexane) |
| 86 | Ph |  | H | Single bond | 0 | 143-145 (diethylether – n-hexane) |
| 87 | nBu |  | H | Single bond | 0 | 46-48 (ethyl acetate – n-hexane) |

(0104)

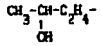
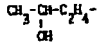
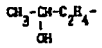
Table 2 (continued)

| Example No. | R1 | R2 | R3 | A | n | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|
| 88 | nBu |  | H | Single bond | 0 | 108-110 (n-hexane) |
| 89 | nBu |  | H | Single bond | 0 | 92.5-94.5 (n-hexane) |
| 90 | nBu |  | H | Single bond | 0 | 106-108 (n-hexane) |
| 91 | nBu |  | H | Single bond | 0 | 123-125 (ethanol – n-hexane) |
| 92 | nBu |  | H | Single bond | 0 | 123-125 (diethylether – n-hexane) |
| 93 | nBu |  | H | Single bond | 0 | 139-140 (ethanol – n-hexane) |
| 94 | nBu |  | H | $CH_2$ | 0 | 121-123 (ethyl acetate – n-hexane) |
| 95 | nBu |  | H | -CH=CH- | 0 | 194-196 (ethanol – n-hexane) |
| 96 | nBu |  | H | Single bond | 1 | 222 (decomposition) (ethanol – n-hexane) |
| 97 | Ph |  | H | Single bond | 1 | 250 (decomposition) (methanol – n-hexane) |
| 98 | nBu |  | H | Single bond | 1 | 247 (decomposition) (ethanol – n-hexane) |

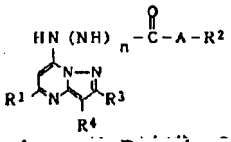
**(0105)**

Table 2 (continued)

| Example No. | R1 | R2 | R3 | A | n | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|
| 99 | Ph |  | H | Single bond | 1 | 263 (decomposition) (ethanol – n-hexane) |
| 100 |  |  | H | Single bond | 0 | 128-130 (methylene chloride – n-hexane) |
| 101 |  |  | H | Single bond | 0 | 153-155 (ethanol – n-hexane) |
| 102 |  | | H | Single bond | 0 | 127-129 (ethyl acetate - n-hexane) |

**(0106)**

Table 3



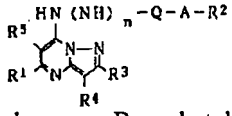
Me: methyl group, nBu: n-butyl group.

| Example No. | R1 | R2 | R3 | R4 | A | n | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|---|
| 103 | nBu |  | Me | Cl | Single bond | 0 | 106-108 (ethanol – n-hexane) |
| 104 | nBu |  | H | Cl | Single bond | 0 | 142-143 (ethanol – n-hexane) |
| 105 | nBu |  | H | Br | Single bond | 0 | 146-148 (ethanol – n-hexane) |
| 106 | nBu |  | H | Cl | Single bond | 0 | 133-135 (diethylether – n-hexane) |

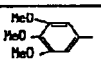
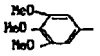
 

(0107)

Table 4

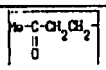
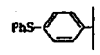
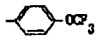
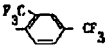


Me: methyl group, Et: ethyl group, nBu: n-butyl group, Ph: phenyl group.

| Example No. | R1 | R5 | R2 | R3 | R4 | Q | A | n | Melting point (° C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|---|---|---|
| 107 | H | H |  | H | H | C=O | Single bond | 0 | 185-187 (methylene chloride – n-hexane) |
| 108 | nBu | H |  | Me |  | C=O | Single bond | 0 | 138-140 (ethyl acetate – n-hexane) |
| 109 | nBu | H |  | nBu | H | C=O | Single bond | 0 | 95-97 (ethyl acetate – n-hexane) |
| 110 | nBu | H |  | nBu | Me | C=O | Single bond | 0 | 96-98 (ethyl acetate – n-hexane) |
| 111 | nBu | H |  | Ph | H | C=O | Single bond | 0 | 190-192 (methylene chloride – diethylether) |
| 112 | nBu | H |  | Ph | $PhCH_2$- | C=O | Single bond | 0 | 149-151 (ethyl acetate – n-hexane) |
| 113 | nBu | H |  | Ph |  | C=O | Single bond | 0 | 111-113 (ethyl acetate – n-hexane) |
| 114 | nBu | H |  | H | nBu | C=O | Single bond | 0 | 81-83 (n-hexane) |
| 115 | nBu | H |  | H | Ph | C=O | Single bond | 0 | 139-141 (ethyl acetate – n-hexane) |

(0108)

Table 4 (continued)

| Example No. | R1 | R5 | R2 | R3 | R4 | Q | A | n | Melting point (° C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|---|---|---|
| 116 | nBu | Me |  | H | H | C=O | Single bond | 0 | 145-147. (methylene chloride - n-hexane) |
| 117 | -$CH_2CH_2CH_2CH_2$- | |  | H | H | C=O | Single bond | 0 | 102-104 (methylene chloride - – n-hexane) |
| 118 |  | H |  | H | H | C=O | Single bond | 0 | 115-117 (methylene chloride - – n-hexane) |
| 119 | Et-S-$CH_2$- | H |  | H | H | C=O | Single bond | 0 | 80-82 (ethyl acetate – n-hexane) |
| 120 | MeS-$CH_2CH_2$- | H |  | H | H | C=O | Single bond | 0 | 113-115 (methylene chloride - diethylether) |
| 121 |  | H |  | H | H | C=O | Single bond | 0 | 179-181 (methylene chloride - diethylether) |
| 122 | nBu | H |  | H | H | C=O | Single bond | 0 | 98-100 (diethylether) |
| 123 | nBu | H |  | H | H | C=O | Single bond | 0 | 73-75 (n-hexane) |
| 124 | nBu | H |  | H | H | C=O | Single bond | 0 | 129-131 (n-hexane) |
| 125 | nBu | H |  | H | H | C=O | Single bond | 0 | 91-93 (diethylether – n-hexane) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 126 | nBu | H |  | H | H | C=O | Single bond | 0 | 91-93 (n-hexane) |

**(0109)**

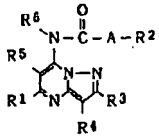
Table 4 (continued)

| Example No. | R1 | R5 | R2 | R3 | R4 | Q | A | n | Melting point (° C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|---|---|---|
| 127 | nBu | H | Ph | H | H | $SO_2$ | Single bond | 0 | over 300°C (ethyl acetate – n-hexane) |
| 128 | nBu | H |  | H | H | $SO_2$ | Single bond | 0 | over 300°C (ethyl acetate – n-hexane) |

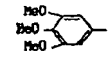
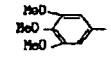
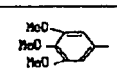
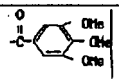
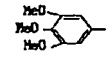
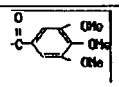
 

(0110)

Table 5



Me: methyl group, nBu: n-butyl group.

| Example No. | R1 | R5 | R2 | R3 | R4 | R6 | A | Melting point (°C) (Re-crystallisation solvent) |
|---|---|---|---|---|---|---|---|---|
| 129 | nBu | H |  | H | H | Me | Single bond | 93-95 (ethyl acetate – n-hexane) |
| 130 | nBu | H |  | H | H | Ph-$CH_2$- | Single bond | $^1$H-NMR(CDCl$_3$) δ 0.76(3H,t,J=7.2), 0.9-1.1(2H,m),1.3-1.4(2H,m), 2.51(2H,t,J=7.4), 3.47(6H,s), 3.74(3H,s), 5.33(2H,brs), 5.83(1H,s), 6.60(2H,s), 6.68(1H,d,J=2.0), 7.1-7.3(5H,m), 8.28(1H,d,J=2.0) |
| 131 | nBu | H |  | H | H |  | Single bond | 127-129 (ethyl acetate – n-hexane) |
| 132 | nBu | H |  | H | H |  | Single bond | 119-121 (diethylether – n-hexane) |
| 133 | Me | H |  | H | H |  | Single bond | 180-182 (methylene chloride - – n-hexane) |
| 134 | nBu | H |  | H | H |  | Single bond | 111-113 (diethylether – n-hexane) |

(0069)

Table 6

| Test Compound (Example No.) | Inhibition rate (%) |
|---|---|
| 7 | 74.6 |
| 15 | 66.9 |
| 16 | 44.7 |
| 18 | 58.0 |
| 19 | 83.0 |
| 23 | 43.1 |
| 26 | 62.3 |
| 52 | 64.7 |
| 53* | 48.9 |
| 55 | 44.5 |
| 75 | 66.7 |
| 100 | 44.9 |
| 111** | 32.2 |
| 115 | 57.2 |

*: Compound concentration = 10 μM

**: Compound concentration = 3 μM

Brief Description of the Figures

**Figure 1**

Figure 1 comprises graph showing inhibition effect of iNOS induction by LPS of effective ingredient compound of this invention determined according to Pharmacological Test Example 2.

**Figure 2**

Figure 2 comprises graph showing inhibition effect of iNOS induction by IL-1β of effective ingredient compound of this invention determined according to Pharmacological Test Example 2.

**Figure 1**

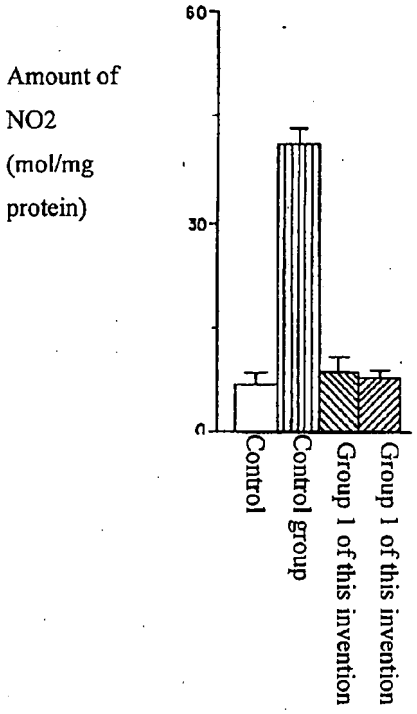
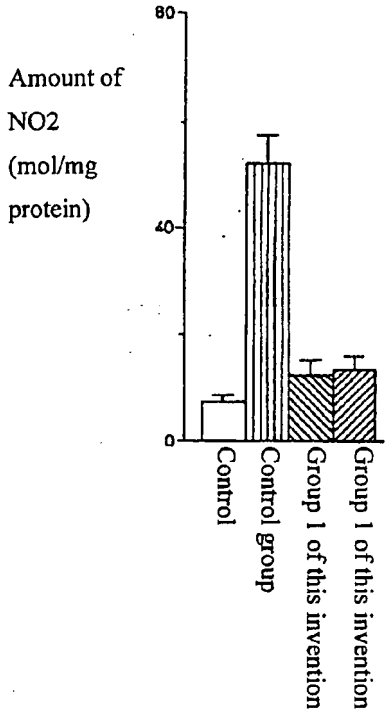



**Figure 2**



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